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To Members of the Secretaries' Science Advisory Board,

I am writing to you regarding contaminants of emerging concern (CECs) and how the State of North Carolina assesses the potential human health risks associated with CECs and communicates that potential health risk to the public. I applaud the NC Department of Environmental Quality (DEQ) and the NC Department of Health and Human Services (DHHS) and their staff for recognizing the potential importance of CECs and attempting to ensure that the public and our environment are adequately protected from potential adverse effects associated with these chemicals. However, I have serious concerns about how the state has issued and communicated a provisional health advisory (or health goal) for the chemical GenX that has been found in the Cape Fear River and I believe my concerns are symptomatic of a more general problem in how the state addresses these issues. Thus, I am pleased to see that the Secretaries of the DEQ and DHHS have appointed you to the Science Advisory Board (SAB) to help them address the issue of CECs in North Carolina. Below I provide a brief basis for my concerns in this matter and my recommendations for how the state can move forward in a more transparent and scientifically defensible manner.[1] I hope that you will consider these recommendations and I see no reason why these, or something similar, cannot be implemented expeditiously so that the public can be properly and promptly informed about potential health risks associated with CECs in North Carolina.

By way of introduction, I have been a Professor of Environmental Chemistry and Toxicology at North Carolina State University (NCSU) since 1993. My expertise lies in the sources, detection, behavior and fate of chemicals in the environment and the potential adverse effects these chemicals may have on human health and the environment. Over my 25 years at NCSU, I have served as Head of the Department of Environmental and Molecular Toxicology (2001-2006), Head of the Departments of Zoology and Biology (2006-2011), Leader of the NCSU Global Environmental Change and Human Well-being initiative, among other leadership positions. I also have substantial experience with environmental and toxicological studies in NC, including work at eight NC Superfund sites, assisting the State of NC with assessing chemical risks following Hurricanes Fran and Floyd, assessing chemical exposure in 15 of NC's 17 River Basins, and working in collaboration with five state agencies (NCDEQ, NCDHHS, NCDOT, NCWRC and NCDA&CS) on various chemical exposure and toxicity issues in the state. I have not been involved with any of the work related to GenX in NC, but I am currently conducting several studies on per- and polyfluoroalkyl substances (PFAS) in China and in my research laboratory at NCSU.

To place my concerns in context, I want to suggest that the State of NC set Human Health Goals

1. in a transparent and scientifically defensible manner
2. based only on data relevant to human health
3. using the best available data and scientifically proven and acceptable analysis methods

It is my opinion that the State of NC did not adequately follow these three principles when they set the provisional health goal for GenX and I am concerned that future health goals for other chemicals may also be improperly derived if the state does not revise their process to adhere to these principles.

[1]Chemours has retained me to review technical information regarding GenX and the possible human health effects associated with GenX. That has led me to write this letter on GenX and the broader issue of assessing human health risks to CEC exposure. The views I express in this letter are my own. In addition, no endorsement by my employer, NCSU, is implied.

The State of NC should set Human Health Goals in a transparent and scientifically defensible manner.

National water quality criteria (WQC), water quality standards (WQS) and maximum contaminant levels (MCL) all have a rigorous process of data review and analysis, publication of draft values with extensive documentation supporting those values, peer scientific review and response to that review, and public comment and response to those comments, prior to the issuance of a value designed to protect human health. CECs, by their very nature, often do not have all of the data needed to derive these formal criteria or standards. In the absence of these standards or other formal guidance for CECs, the State of NC can consider establishing state-specific health goals designed to represent a "level of contamination below which no adverse health effects would be expected over a lifetime of exposure".[2] As discussed by Dr. Zack Moore (NC State Epidemiologist) in a presentation to the Secretaries' Science Advisory Board (SAB) on 4 December 2017, the requirements to establish a health goal in NC include "***sufficient*** health-related information" and the specific requirement for animal studies.[3]

These animal studies also need to be ***sufficient*** and ***relevant to humans*** to be considered in deriving a health goal. As I will point out below, the portion of the animal studies relied upon by the state to derive the GenX provisional health goal is ***not relevant to humans*** and a scientific peer review would have identified this problem. This situation is not unlike that which the state found itself in with the issuance in 2015 of the chromium health goal for drinking water that was then rescinded in 2016, although different scientific issues were involved.[4] The state has now asked the SAB to review the chromium, GenX and other CEC issues[5,6] and this is an excellent step toward retrospectively correcting the current problems with the state's process for issuing health goals. However, the state still needs to allow for and consider review and comment from other scientists and the public prior to issuing health goals, even provisional ones.

Although a health goal is non-regulatory and non-enforceable[7] it is also an important benchmark for the public, including public utilities and others making decisions regarding water use, treatment, etc. Given the importance that the public places on the health goal and in the particular case of GenX – the widespread concern that this provisional health goal has generated – it is incumbent upon the state to carefully review the available human health related data to ensure that the standard of ***sufficient*** is met and that all data used are appropriate and relevant for this purpose. In addition, even if there is insufficient information on a CEC like GenX to derive a WQC or MCL, that is no reason to circumvent the transparent and scientifically defensible process used to review and analyze available data, and consider and respond to comments from the scientific and public communities.

The provisional health goal released by the state for GenX, and its subsequent revision, did not follow a rigorous, transparent and scientifically defensible process. While the retroactive review by the SAB is a step in the right direction, it is not sufficient, and in the meantime a provisional health goal for GenX that has not been subject to proper review and is not scientifically defensible remains active and is driving current decision making regarding GenX in the Cape Fear River Basin.

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[2] Presentation by Dr. Zack Moore, NC State Epidemiologist to the Secretaries' Science Advisory Board (SAB) on 4 December 2017. https://files.nc.gov/ncdeq/GenX/SAB/GenX%20Health%20Studies%20and%20Advisories%20SSAB%2012_4_2017.pdf

[3] Presentation by Dr. Zack Moore, NC State Epidemiologist to the Secretaries' Science Advisory Board (SAB) on 4 December 2017.

[4] https://deq.nc.gov/press-release/despite-mischaracterizations-north-carolina-protecting-drinking-water

[5] https://deq.nc.gov/news/hot-topics/genx-investigation/secretaries-science-advisory-board.

[6] https://files.nc.gov/governor/documents/files/Science%20Advisory%20Board%20Charter.pdf

[7] Presentation by Dr. Zack Moore, NC State Epidemiologist to the Secretaries' Science Advisory Board (SAB) on 4 December 2017.

The State of NC should set Human Health Goals based only on data relevant to human health.

When an organism is exposed to chemicals in a high enough dose or concentration, adverse toxic effects can occur by following different pathways. Different species are known to have different susceptibilities along these pathways. For example, while vertebrates can metabolically activate certain chemicals (e.g., aromatic hydrocarbons) to make them more toxic within their bodies, invertebrates have very limited ability to activate these chemicals and thus they are far less susceptible to having toxic effects from exposure to these chemicals. Similarly, even within vertebrates, these interspecies differences have been known for a long time and we are still discovering how important these differences can be. This is why in human health risk assessments, it is common to build in an uncertainty factor (or safety factor) to account for possible differences between test animals (e.g., rodents) and humans for an *interspecies* safety factor, just as there is an additional safety factor to account for possible *intraspecies* differences within the human population. The assumption here is that humans ***might*** be more susceptible to a chemical than a rodent and – ***without knowing any more*** – a 10-fold interspecies safety factor is applied to provide additional protection against this ***uncertainty***. In the case of potential toxicity of GenX to rodents versus humans, we actually do know a lot more and it relates to the specific pathway that GenX causes liver toxicity, including tumors, in rodents. This pathway involves a nuclear receptor called peroxisome proliferator-activated receptor alpha (***PPARα***) and chemical toxicity that follows this pathway is called ***PPARα-dependent***.

Since at least 2004, it has been well known that rodents are far more sensitive than humans to PPARα-dependent liver toxicity and there was a scientific consensus that it is unlikely that PPARα-dependent tumors found in rodents would occur in humans.[8] Since that time an overwhelming body of evidence has confirmed the lack of human relevance for PPARα-dependent liver toxicity and tumors. This evidence was recently summarized in a review published in Archives of Toxicology and entitled ***The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions.***[9] The lead author of the study is a scientist from the US EPA in Research Triangle Park, NC and a leading authority on how chemicals induce liver toxicity. As the title of this paper states, liver tumors produced by chemicals in rodents by way of the PPARα pathway are not relevant to human health. The details and dozens of peer-reviewed papers supporting this conclusion are provided in this paper. This conclusion of non-human relevance of ***PPARα-dependent*** liver toxicity in rodents is not surprising given similar conclusions from a different EPA scientist over 10 years ago.[10]

The lack of human relevance to ***PPARα-dependent*** liver toxicity in rodents is critically important to assess the potential human health effects of exposure to GenX because both the initial and revised provisional health goals issued by the DHHS for GenX were derived from ***PPARα-dependent*** liver toxicological effects in rodent studies. The initial DHHS provisional health goal was based on a Key 2-year chronic study[11] and the revised provisional DHHS health goal was based on a 28-day subchronic study[12]. The studies themselves stated that "most test substance-related effects were consistent with a peroxisome proliferator (PPARα agonist)".[13] Thus, the liver toxicity data from these studies, and used by the DHHS, do not meet the human relevance criteria for use in

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[8] Lai DY. 2004. Rodent Carcinogenicity of Peroxisome Proliferators and Issues on Human Relevance. Journal of Environmental Science and Health, Part C, 22:37-552004. https://doi.org/10.1081/GNC-120038005.

[9] Corton C, Peters JM, Klauning JE. 2017. The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Archives of Toxicology. https://doi.org/10.1007/s00204-017-2094-7.

[10] Lai DY. 2004. Rodent Carcinogenicity of Peroxisome Proliferators and Issues on Human Relevance. Journal of Environmental Science and Health, Part C, 22:37-552004. https://doi.org/10.1081/GNC-120038005.

[11] https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/6/2/?documentUUID=84f751a2-e4d0-418c-8103-6f0e18cd7069.

[12] https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/6/2/?documentUUID=7fde65ec-5187-42ef-8e05-58436035a555.

[13] https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/6/2/?documentUUID=7fde65ec-5187-42ef-8e05-58436035a555.

setting human health goals. It is possible that some non-***PPARα-dependent*** changes in clinical chemistry were observed at very high doses in the 2-year chronic study, but using these clinical chemistry endpoints would yield an even higher health goal than the original value issued by DHHS.[14]

Thus, the State of NC inappropriately relied on ***PPARα-dependent*** liver toxicity in rodents – results that lack human relevance – in setting the provisional health goal for GenX.

The State of NC should set Human Health Goals using the best available data and scientifically proven and acceptable analysis methods.

As explained above, rodent ***PPARα-dependent*** toxicity lacks human relevance and is inappropriate for use as an effect for human health risk assessments. In addition, the process that DHHS used to revise the provisional health goal is very concerning. DHHS initially used a complete 2-year chronic study in rats that looked at both chronic toxicity and cancer. This study was identified by the European Union (EU) as the Key Study that existed for GenX.[15] Five other GenX toxicity studies were considered by the EU but rejected as a Key Study because they did not provide the quality and quantity of information needed for a Key Study. The DHHS subsequently revised the provisional health goal, rejecting the Key Study identified by the EU (and also used initially by the DHHS) and instead used one of the studies that was a far shorter (subchronic 28 day) and less complete toxicity study. To my knowledge there has been no scientific justification provided for rejecting the Key 2-year chronic study and replacing it with a 28-day subchronic study, but this switch resulted in a **100-fold decrease** in the provisional health goal value. Although the issue is really moot for GenX because neither of these ***PPARα-dependent*** rodent-study results have human relevance, the seemingly arbitrary switch from what would be considered the best available data (a complete 2-year chronic study) to a far less complete 28-day subchronic study is not scientifically defensible. Furthermore, replacing the chronic study with a subchronic study adds an additional 10-fold safety factor that is not necessary with the original chronic study. In essence, the state substituted an inferior study for the original superior study and then added an additional 10-fold safety because they are now using an inferior study. This also is not scientifically defensible.

The human health risk assessment of CECs is a complex task made more difficult by having less information than we have for most regulated chemicals. This does not mean that we should not try to assess potential risk in the most scientifically appropriate manner. Furthermore, we should make assessments, even provisional non-enforceable assessments, based on adequate and appropriate data. It is not possible for me to cover all of the details of the risk assessment process of CECs in general, or of GenX in particular, in this letter. However, I would be pleased to engage the SAB in any manner you deem appropriate to offer assistance in this very important endeavor.

Sincerely,

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Cc: DHHS Secretary Mandy K. Cohen
DEQ Secretary Michael S. Regan

[14] Caverly Rae JM, Craig L, Slone TW, Frame SR, Buxton LW, Kennedy GL. 2015. Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in Sprague–Dawley rats, Toxicology Reports, Volume 2, 2015, Pages 939-949, ISSN 2214-7500, https://doi.org/10.1016/j.toxrep.2015.06.001.
[15] https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/6/2/?documentUUID=84f751a2-e4d0-418c-8103-6f0e18cd7069.